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(54) Title: N,N–BIS (PHENYLCARBAMOYLMETHYL) DIMETHYLAMMONIUM CHLORIDE AND DERIVATIVES IN THE TREATMENT OF PAIN

(57) Abstract

N,N–Bis (phenylcarbamoylmethyl) dimethylammonium chloride and derivatives thereof were found to be useful in the treatment of pain while avoiding side effects associated with conventional medications.

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N, N-BIS (PHENYLCARBAMOYLMETHYL) DIMETHYLAMMONIUM CHLORIDE AND DERIVATIVES IN THE TREATMENT OF PAIN

BACKGROUND OF THE INVENTION

At present three major classes of drugs are used to manage pain.

The first class of drugs consists of narcotic opiates, such as morphine, which block the perception of pain and act primarily in the brain and spinal cord. Members of this class of drugs are effective and potent but cause severe side effects such as sedation, constipation, and respiratory depression. These drugs are also known to cause severe addiction, which limits their usefulness in patients suffering from moderate pain.

The second class of drugs consists of local anesthetics which prevent pain in a specific region by blocking the transmission of signals through nerves. These drugs are given by injection to produce a high local concentration, often around specific sensory nerves to achieve nerve blocks. This type of pain control is practical only for interruption of acute pain and has little or no role in the management of chronic pain.

The third class of drugs consists of non-steroidal anti-inflammatory drugs, the most well known member of this class being aspirin. These drugs relieve pain by blocking the production or action of chemical mediators of pain and are used to control pain of low to moderate intensity.

In addition to the above, there are diverse drugs that have been found to be effective in the treatment of pain of particular etiology: this includes for example specific anti-migraine drugs.

Presently the only useful therapy for the treatment of chronic severe pain are the morphine-like drugs (Class I above) and since this use is limited in the majority of patients, there is an urgent and important need to identify new and alternate analgesic treatments.

SUMMARY OF THE INVENTION

The present invention relates to quaternary ammonium compounds, pharmaceutical compositions containing such compounds as the active ingredient and to a method of treating and/or preventing pain with the same. The compounds of the present invention are certain quaternary ammonium compounds of Formula I, especially N, N-Bis (phenylcarbamoylmethyl) dimethylammonium chloride. It has now been found that these compounds offer potent and long-acting relief from pain when administered either systemically or locally. Furthermore, the side effects of the opiates or opiods (Class I drugs) mentioned above are not caused by the new therapy. The method of the present invention significantly improves the therapeutic alternatives for treating chronic pain and the method is particularly useful in the preventing and/or treating of subjects that have demonstrated erratic effects of conventional therapy. Since the new method also avoids the side effects of drugs used in currently available therapy, the present method provides a safe, effective treatment of long duration for moderate to severe pain, such as for example neuropathic pain.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms have the following meaning:

"Alkyl" refers to a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms and having one point of attachment. Examples include n-propyl (A C_3 alkyl), isopropyl (also a C_3 alkyl) and t-butyl (a C_3 alkyl).

"Alkoxyalkyl" refers to an alkylene group substituted with an alkoxy group. For example, methyoxyethyl ($CH_3OCH_2CH_2$-) and ethoxymethyl ($CH_3CH_2OCH_2$-) are both C_3 alkoxyalkyl groups.

"Alkylene" refers to a divalent radical which is a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms and having two points of attachment. An example is propylene (-$CH_2CH_2CH_2$-), a C_3 alkylene.

"Aralkyl" refers to an alkylene group wherein one of the points of attachment is to an aryl group. An example is the benzyl group ($C_6H_5CH_2$-) , a C_7 aralkyl group.

"Alkanoyloxy" refers to an ester substituent wherein the ether oxygen is the point of attachment to the molecule. Examples include propanoyloxy (CH_3CH_2C=O-O-), a C_3 alkanoyloxy and ethanoyloxy (CH_3C=O-O), a C_2 alkanoyloxy.

"Alkoxy" refers to an O-atom substituted by an alkyl group, for example methoxy (-OCH_3), a C_1 alkoxy.

"Alkoxycarbonyl" refers to an ester substituent wherein the carbonyl carbon is the point of attachment to the molecule. Examples include ethoxycarbonyl (CH_3CH_2OC=O), a C_3 alkoxycarbonyl, and methoxycarbonyl (CH_3OC=0-), a C_2 alkoxycarbonyl.

"Aryl" refers to aromatic groups which have at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl (also known as heteroaryl groups) and biaryl groups, all of which may be optionally substituted. Carbocyclic aryl groups are generally preferred in the compounds of the present invention, wherein phenyl and naphthyl groups are preferred carbocyclic aryl groups.

"Cycloalkyl" refers to a ring, which may be saturated or unsaturated and monocyclic, bicyclic or tricyclic formed entirely from carbon atoms. An example is the cyclopentenyl group (C_5H_7-) which is a five carbon unsaturated cycloalkyl group.

"Carbocyclic" refers to a ring which may be either an aryl ring or a cycloalkyl ring, both as defined above.

"Thioalkyl" refers to a sulfur atom substituted by an alkyl group, for example thiomethyl (CH_3S-), a C_1 thioalkyl.

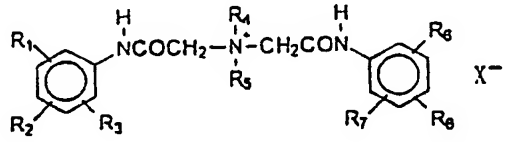
The present invention provides a sustained and effective treatment and/or prevention of pain offered by pharmaceutical compositions comprising one or more of the compounds encompassed within Formula I. This is of significant therapeutic importance, since many patients taking conventional pain medication experience serious side effects as well as erratic therapeutic effects of their medication, particularly

in long-term use of the same. The finding that compounds encompassed within Formula I offer an effective and prolonged therapeutic activity against pain when given either orally or parenterally is unexpected and surprising, given the fact that although compounds encompassed within this formula have chemical similarities with some local anesthetics, the latter compounds do not generally share the analgesic activity of the compounds of the invention.

In contrast to the opiates and opiods, the compounds of Formula I do not appear to cause any significant modification to the perception of pain; in contrast to the nerve-blocking activity of local anesthetics, the compounds of Formula I do not indiscriminately block nerve conduction and in contrast to the major compounds of Class 3, are not potent cyclooxygenase inhibitors. Thus, the potent pain inhibition offered by the compounds of the present invention is both surprising and unexpected.

This finding is of significant therapeutic and toxicological importance since the activity of the pain treatment is improved with the new method, and the conventional toxicity of pain medication will be largely avoided by the treatment of the patient according to the present invention.

Formula I is represented by the following formula:



wherein R_1, R_2, R_3, R_6, R_7 and R_8 are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7-alkanoyloxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2- C_7-

alkoxycarbonyl, N(R_9, R_{10}), phenyl and C_1-C_6-thioalkyl; and where R_9 and R_{10} are independently hydrogen, acetyl, methanesulfonyl, or C_1-C_6-alkyl; R_4 and R_5 are independently selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 alkoxyalkyl and C_7-C_{12} aralkyl; X is the anion of a pharmaceutically acceptable salt; and isolated enantiomeric, disasteriomeric and geometric isomers thereof, and mixtures thereof.

A preferred compound of the present invention is a compound of Formula I wherein R_1, R_2, R_3, R_6, R_7 and R_8 are each hydrogen, R_4 and R_5 are each methyl and X is chloride anion. This compound ("Compound I") was synthesized as described in Belgium Patent No. 614,154, by Traunt and Dahlborn, 1962, which follows the Swedish patent 1779/61, the disclosure of which is herein incorporated by reference (see also T. Takahashi, J. Okada, M. Hori, A. Kato, K. Kanematsu, and Y. Yamamoto, *J. Pharm. Soc. Japan 76,* 1180-6 (1956)). A conventional route for synthesis involves three (3) steps and can be described (as in the aforementioned patent) as follows:

i) Chloroacetanilide

To a chilled solution of aniline (37.2 g, 0.40 mol) and potassium carbonate (66.4 g, 0.48 mol) in chloroform (200 ml) was added dropwise via cannula a solution of chloroacetylchloride (49.6 g, 0.44 mol) in chloroform (100 ml) and the reaction mixture was heated to 55°C for 90 minutes. To the cooled reaction mixture was then added water (300 ml) , the organic layer was collected and the aqueous layer was extracted twice more with chloroform (2 x 100 ml). The combined organic layers were dried over sodium sulfate and evaporation of the solvent in vacuo provided the crude product. The product was purified via extraction through a Soxhlet apparatus with diethyl ether to provide 22.7 g of the desired chloroacetanilide. m.p. 133-135°C, ^{1}H NMR ($CDC1_3$, 200 MHz) δ : 8.3 (br. s, NH, 1H) , 7.6-7.1 (m, Ar, 5H) 4.1 (s, CH_2, 2H).

ii) Dimethylaminoacetanilide

A mixture of chloroacetanilide (10.0 g, 59 mmol) in dimethylamine, 40% wt in water (100 ml) was refluxed for 4 hours. The cooled reaction mixture was partitioned between dichloromethane (100 ml) and 1M NaOH aqueous solution (100 ml). The aqueous layer was extracted twice more with dichloromethane (2 x 100 ml), the combined organic layers were concentrated in vacuo to a volume of approximately 100 ml and washed

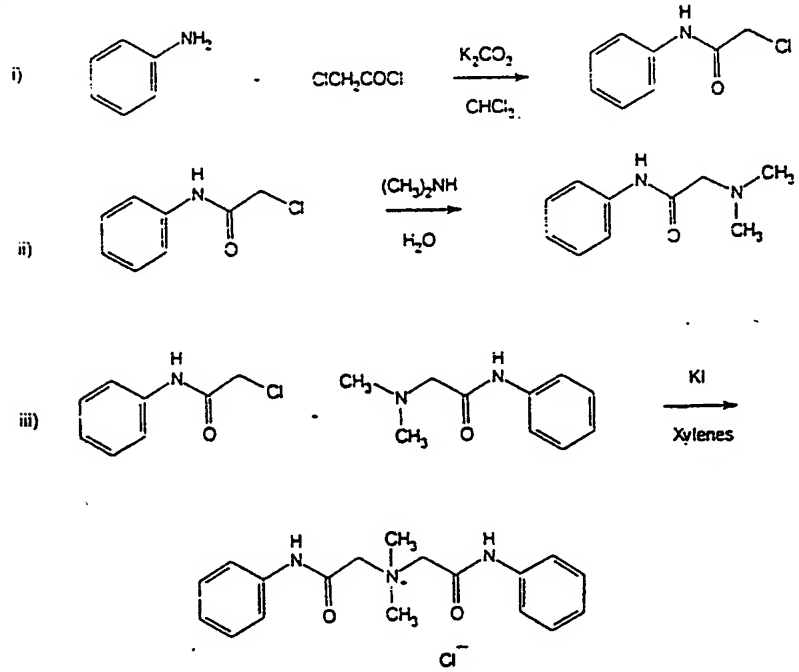
with water (2 x 100 ml) in order to remove the remaining dimethylamine. The organic layer was collected, dried over sodium sulfate and the solvent evaporated in vacuo to provide 10.2 g (97% yield) of the pure dimethylaminoacetanilide. ^{1}H NMR ($CDC1_3$, 200 MHz) δ : 9.1 (br. s, NH, lH), 7.6-7.0 (m, Ar, 5H) 3.1 (s, CH_2, 2H) , 2.4 (s CH_3, 6H)

iii) N,N-Bis- (phenylcarbamoylmethyl) dimethylainmonium chloride

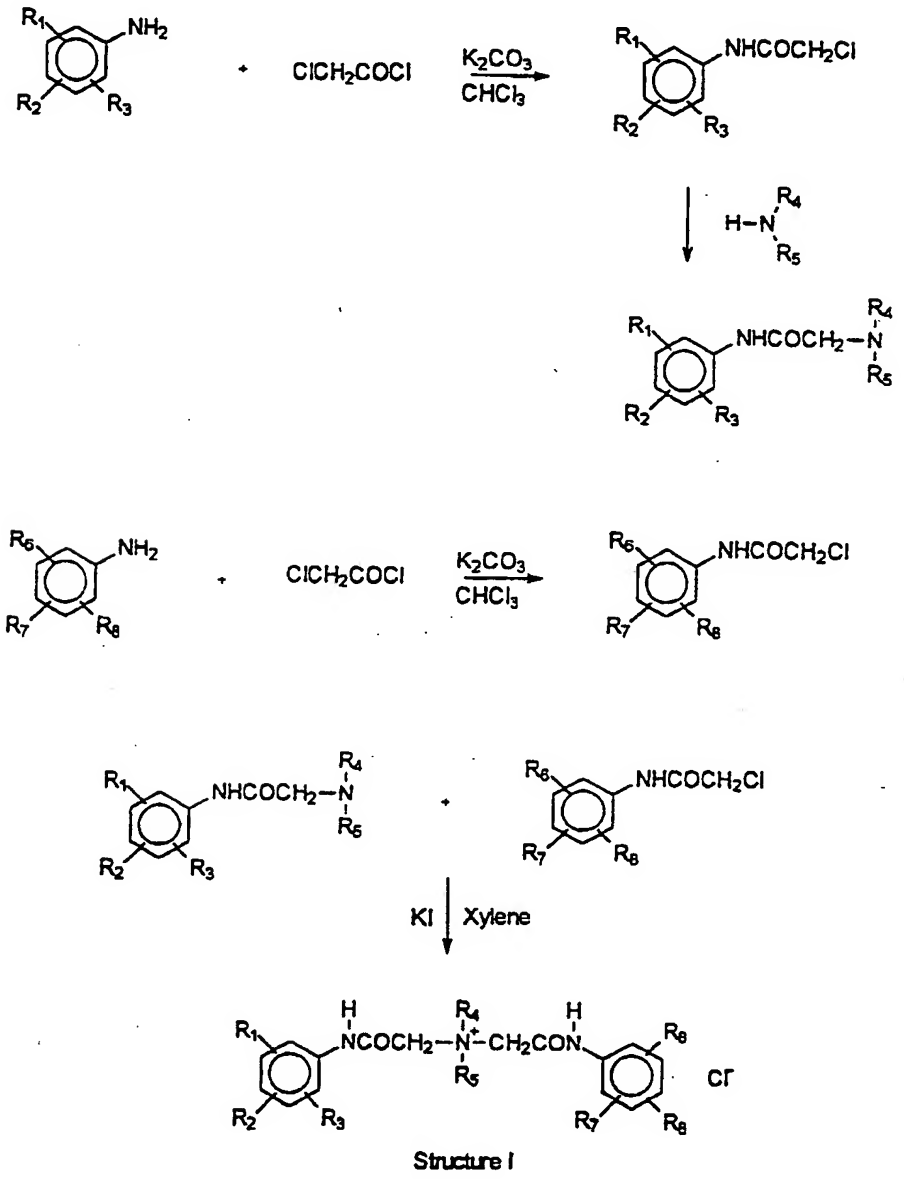
A mixture of chloroacetanilide (10.1g, 59.5 mmol), dimethylaminoacetanilide (10.7 g, 60 mmol) and potassium iodide, 99+% (0.1 g, 0.6 mmol) in dry xylene (30 ml) was refluxed for 1 hour and then allowed to stand overnight to ambient temperature. The solvent was decanted and the remaining gummy solid was triturated in diethyl ether in order to obtain a whitish powder. The resulting solid was collected and recrystallized in a mixture of ethanol and diethyl ether to provide 9.3 g (45% yield) of the desired ammonium salt. m.p. 177-178°C, ^{1}H NMR (DMSO-d_6, 300 MHz) δ:11.3 (s, NH, 2H) , 7.7-7.1 (m, Ar, 10 H) 4.8 (s, CH_2, 4H) , 3.6 (s CH_3, 6H), ^{13}C NMR (DMSO-d_6 75 MHz) δ:162.1(+), 137.8 (+), 128.8 (-), 124.3 (-), 119.7 (-), 63.0 (+), 52.8 (-), LRMS(EI) m/z=297 (0.95%, M^+-CH3), elemental analysis calculated for $C_{18}H_{22}N_4O_2C1$ (347.84): C, 62.15; H, 6.37; N, 12.08; found C, 61.75; H, 6.50; N, 12.04.

Reference: A.P. Traunt and J.R. Dahlbom Belgium Patent No. 614154, Feb. 20, 1961.

Synthetic Scheme:



Other compounds encompassed by Formula I can be synthesized in an analogous manner and are within the skill in the art. A typical synthetic scheme is as follow:



Structure I

Suitable pharmaceutically acceptable salts include acid addition salts of acids such as hydrochloric, hydrobromic, benzenesulfonic (besylate), benzoic, camphorsulfonic, ethanesulfonic, fumaric, gluconic, glutamic, isethionic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pathothenic, succinic, p-toluenesulfonic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid, although the preferred acid addition salt is the hydrochloride salt.

The magnitude of the prophylactic or therapeutic dose of the compounds of the present invention in the acute or chronic management of pain will vary with the severity and nature of the condition being treated and the route of administration. The dose and the frequency of the dosing will also vary according to age, body weight and response of the individual patient. In general, the total daily dose range for the compounds of the present for the conditions described herein is from about 10 mg to about 20 mg in single or repeated doses, preferably in repeated doses. In managing the patient, the therapy should be initiated at a lower dose, perhaps at about 10 mg to about 50 mg, and may be increased up to about 200 mg depending on the patient's global response. For pharmacokinetic reasons, it may also be preferred to administer an initial loading (bolus) dose of the drug to patients suffering from pain. It is further recommended that patients be titrated, based on individual response(s). It may be necessary to use dosages outside these ranges, as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust or terminate therapy in conjunction with individual patient response. The terms "a therapeutically effective amount" and "an amount sufficient to treat pain syndrome but insufficient to cause adverse effects" are encompassed by the above-described dosage amounts and dose-frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the compounds of the present invention. For example, oral, sublingual, rectal, parental (subcutaneous, intramuscular, intravenous, etc.), transdermal, topical and like forms of administration may be employed. Dosage forms include but are not limited to solid dosage forms, suspensions, solutions, creams, gels or elixers. For example, tablets, troches, dispersions, suspensions, solutions, capsules, microencapsulated systems, sprays, topical delivery systems, and the like are suitable. Because of their ease of administration, tablets and capsules represent some of the more advantageous oral dosage unit forms, in which case solid pharmaceutical

carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set forth above, the compounds of the present invention also may be administered by controlled release means and delivery devices such as those described in U.S. Patent Nos. 3,845,770, 3,916,899, 3,536,809, 3,598,123 and 4,008,719, and PCT application 1) 92/20377, the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete unit dosage forms such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent1 surface active agent or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent, All of the foregoing techniques are well known to persons of skill in the pharmaceutical art. Each tablet may contain from about 5 mg to about 200 mg of the active ingredient.

The pharmaceutical compositions of the present invention comprise the compounds of the present invention as the active ingredient, including pharmaceutically acceptable salts thereof, and may also contain a pharmaceutically acceptable carrier, and optionally other therapeutic ingredients and conventional additives, including aqueous based carriers, co-solvents such as ethyl alcohol, propylene glycol and

glycerin, fillers, lubricants, wetting agents, flavoring agents, coloring agents, emulsifying, suspending or dispersing agents, suspending agents, etc.

The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic acids. Suitable pharmaceutically acceptable acid addition salts for the compound of the present invention include acetic, benzene sulfonic (besylate), benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pathothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, and the like. The hydrochloride salt is particularly preferred.

In the method of the present invention, the compounds of the present invention can be administered together with one or more other compound(s), most often a conventional pain medication belonging to any of the classes mentioned above, Compounds that improve or prolong the therapeutic effect of the compounds of the present invention, e.g., compounds that inhibit the metabolic or chemical degradation of the compounds of the present invention, may also be co-administered to patients. The two (or more) drugs (compounds of Formula I and one or more other drugs) can be administered in one composition or as separate entities. For example, they can be administered in a single formulation, such as a capsule, tablet, powder, or liquid, mist aerosol, injection, etc. or as separate formulations. The components included in a particular formulation, in addition to the compound(s) of Formula I and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in table form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer) A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent. A composition to be administered rectally may include the combination of drugs consisting of one or more compounds of the present invention and for example at least one additional drug selected from the group consisting of analgesics, local anesthetics, antihistamines, antiserotonergics, metabolic inhibitors, and other agents with synergistic pharmacological efficacy.

In general, according to the method of the present invention, one or more of the compounds of Formula I, alone or in combination with another drug or drugs, is administered to an individual suffering from pain, periodically or continuously, as necessary to manage or eliminate pain and to improve the quality of life.

Examples of suitable administration for various types of pain are as follows:

(a) Local application.

(1) Pain consequent to joint surgery may be averted by intraarticular injections of a pharmaceutically acceptable composition containing one or more compounds of Formula I in concentrations of 0.1% to 5%.

(2) Arthritic pain or pain of bursitis will successfully be treated by similar injections as above.

(3) Pain of burns also can be successfully treated since the degree of analgesia offered by the compounds of Formula I will block the excruciating pain associated with dressing changes.

(4) Pain from an eye infection or trauma will successfully be treated by similar applications of the compounds of the present invention as above.

(b) Systemic administration

Systemic administration of the compounds of the present invention generally results in analgesia without the adverse side effects known for analgesic compounds of the Classes 1, 2 and 3, as stated above. This type of administration may be particularly useful in the treatment and/or prevention of pain associated with cancer, diabetes and a variety of neurological diseases as well as pain associated with burns, surgery, and trauma. It may be particularly useful in the treatment of patients suffering from various neuropathic pain syndromes.

(c) Intravenous regional anesthesia of the extremities

Intravenous regional analgesia of limbs in surgery may be achieved with the compounds of the present invention, its advantage over presently used local

anesthetics being the absence of central nervous system toxicity and the other side effects when the drug is released into the circulation after the completion of surgery. The "release toxicity" of local anesthetics limits the use of regional anesthesia to upper limb surgery, a constraint that does not apply with the use of the analgesic compound of this invention.

The following examples indicate the therapeutic usefulness of the compounds of the present invention, although the present invention is not limited to these examples.

EXAMPLE 1

The compound used in the present invention is the compound of Formula I wherein R_1, R_2, R_3, R_6, R_7 and R_8 are each hydrogen, R_4 and R_5 are each methyl, and X is chloride anion ("Compound I").

ORAL UNIT DOSAGE FORMULATION

Tablets

Ingredients	per tablet	per batch of 10,000 tablets
Compound I	25 mg	250 g
Microcrystalline cellulose	30 mg	300 g
Lactose	70 mg	700 g
Calcium stearate	2 mg	20 g
FD&C Blue # Lake	0.03 mg	300 mg

The selected compound of the present invention is blended with the lactose and cellulose until a uniform blend is formed. The lake is added and further blended. Finally, the calcium stearate is blended in, and the resulting mixture is compressed into tablets using a 9/32 inch (7 mm) shallow concave punch. Tablets of other strengths may be prepared by altering the ratio of active ingredient to the excipients or to the final weight of the tablet.

The surprising utility of the compounds of the present invention has been established by the following studies.

EXAMPLE 2

1. Acute Toxicity in Mice, Rats and Rabbits

The experiments were carried out on animals that were administered intravenously or orally escalating doses of the test compounds. After administration of Compound I, the survival dose values (LD_{50}) were 125 mg/kg after intraperitoneal administration to mice, 264 mg/kg after subcutaneous injection to mice, 150 mg/kg after intraperitoneal administration to rats, 117 mg/kg after oral administration to mice and 17 mg/kg after intravenous administration to rabbits.

Toxicity (LD_{100}) in other mammals was reported by Marchetti et al. to be 36 mg/kg in guinea pig after intravenous administration and 50 mg/kg in rabbit after intravenous administration. (G. Marchetti, L. Merlo, L. Lombardi and M. Cicardi, Arch. Ital. Sci. Farmacol. 14(1), 33-45 (1964)).

2. Systemic Analgesic Effects

The analgesic efficacy of compounds of Formula I was established by the following studies.

2.1. Formalin Paw Test (D. Dubuisson and S.J. Dennis, Pain, 1977, 4 161 174)

In this test a hind paw (footpad) of conscious mice was injected with a formalin solution, which produced a painful stimulus, to which the mice reacted by licking the foot. Pretreatment of the animal with an effective analgesia reduced the pain and consequently the licking behavior.

The method to demonstrate the analgesic effects of Compound I is briefly as follows. At t=0 minutes, either saline, 10, 20, 40, 80 or 160 mg/kg was injected subcutaneously under the dorsal skin of the neck of a CD-I mouse (n=8 for each dose of Compound I) that weighed in the range of 20-45 grams. At t=60 minutes, formalin (2

different amounts were used in separate studies) was injected into the right hind paw (footpad) of each mouse, and the animal was released into the observation chamber (24-26°C). The mice were videotaped in groups of four for 60 minutes. The observations were made from viewing the videotapes activity, and the investigators looked for the following pain behavioral traits: licking of the right hind paw; lifting and licking of the right hind paw; resting/sleeping/being still; exploring or grooming (F.V. Abbott, K.B.J. Franklin and R.F. Wesbrook, Pain, 1995, 60 191-202). The corresponding behavioral traits were checked and recorded for each animal every two minutes for sixty minutes after the formalin injection.

Results showed Compound I produced a dose related inhibition of the delayed phase of licking, which is indicative of pain relief.

In the study where 30µ1 of 2.5% formalin was injected, the ED_{50} was determined to be 145 mg/kg. In the study where 20 µ1 of 2.0% formalin was injected, the ED_{50} was determined to be 50 mg/kg and more than 80% inhibition was obtained at 160 mg/kg of Compound I. At these doses there was no evident alteration of animal behavior other than the reduced reaction to the noxious stimulus.

2.2. Formalin Tail Test

The protocol of this test is similar to that for the Paw Test described above, except that the injection of formalin was in the dorsal mid-tail region of the mouse instead of the hind paw. Behaviors such as licking of the tail (with and without lifting the tail), grooming, exploring and resting were recorded every two minutes for sixty minutes after injection of formalin (30 µ1 of 2.5% formalin)

Two modes of administration (subcutaneous and oral) of Compound I were studied. Subcutaneous administration of Compound I under the dorsal skin of the neck produced a dose related inhibition of the delayed phase of licking which is indicative of pain relief. The ED_{50} was determined to be 40 mg/kg.

In the oral administration study, CD-1 mice weighing 15-30 grams each (n=8 or 4 for each dose of Compound I) were orally administered with either gum arabic (vehicle), 300 mg/kg or 700 mg/kg Compound I, 60 minutes prior to formalin (2.5%, 30

μ1) _ injection. Behaviors such as licking of the tail (with and without lifting the tail), grooming, exploring and resting were recorded every two minutes for sixty minutes after injection of formalin (30 μ1 of 2.5% formalin). At an oral dose of 700mg/kg, Compound I reduced licking by 62%, while at 300 mg/kg, a reduction of 50% was determined

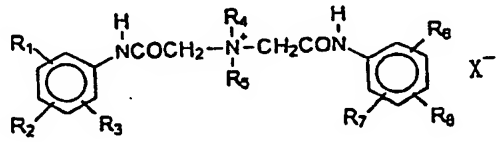
3. Regional Analgesic Effects in Mice

In these experiments a tourniquet is placed around the base of a mouse tail so as to occlude blood flow to and from the tail. Injection of Compound I into the tail vein then rapidly produced block of tail-flick in response to pin-prick but not to heat, which indicates a selective analgesic activity of Compound I. In parallel experiments, lidocaine inhibits responses both to pin-prick and to heat, which indicates a local anesthetic effect of that drug.

4. In experiments using intradermal injections into the human forearm of small volumes of solutions containing Compound I, the drug was found to cause a long-lasting inhibition of pain induced by pin-prick, with little or no effect on sensation of heat or touch, which indicates a selective analgesic activity of the Compound I. Intradermal injections of local anesthetic compounds (examples include lidocaine and bupivacaine) inhibited equally sensation of pain, heat and touch.

What is Claimed Is:

1. A pharmaceutical composition for the treatment and/or prevention of pain, comprising a therapeutically effective amount of a compound of the following formula:



wherein R_1, R_2, R_3, R_6, R_7 and R_8 are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7-alkanoyloxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_7-alkoxycarbonyl, N(R_9, R_{10}), phenyl and C_1-C_6-thioalkyl; and where R_9 and R_{10} are independently hydrogen, acetyl, methanesulfonyl, or C_1-C_6-alkyl; R_4 and R_5 are independently selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 alkoxyalkyl and C_7-C_{12} aralkyl; X^- is the anion of a pharmaceutically acceptable acid; and isolated enantiomeric, disasteriomeric and geometric isomers thereof, and mixtures thereof, together with a pharmaceutically acceptable carrier.

2. The pharmaceutical composition of claim 1, wherein R_1, R_2, R_3, R_6, R_7 and R_8 are each hydrogen, R_4 and R_5 are each methyl, and X^- is chloride anion.

3. The pharmaceutical composition of claim 1, in the form of an oral composition, parenteral composition, topical composition, transdermal composition or rectal composition.

4. The pharmaceutical composition of claim 2, in the form of an oral composition, parenteral composition, topical composition transdermal composition or rectal composition.

5. A method for the treatment and/or prevention of pain in warm-blooded animals including human, comprising administering to said warm-blooded animal in need thereof an effective amount of a compound of the following formula:

wherein R_1, R_2, R_3, R_6, R_7 and R_8 are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7 -alkanoyloxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_7-alkoxycarbonyl, N(R_9,R_{10}), phenyl and C_1-C_6-thioalkyl; and where R_9 and R_{10} are independently hydrogen, acetyl, methanesulfonyl, or C_1-C_6-alkyl; R_4 and R_5 are independently selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 alkoxyalkyl and C_7-C_{12} aralkyl; X^- is the anion of a pharmaceutically acceptable acid; or isolated enantiomeric, disasteriomeric and geometric isomers thereof, or mixtures thereof.

6. The method of claim 5, wherein R_1, R_2, R_3, R_6, R_7 and R_8 are each hydrogen, R_4 and R_5 are each methyl, and X^- is chloride anion

7. The method of claim 5, wherein said compound is administered parenterally, transdermally, rectally, topically or orally.

8. The method of claim 6, wherein said compound is administered parenterally, transdermally1 rectally, topically or orally.

9. The method of claim 5, wherein the pain to be treated or prevented is due to a member selected from the group consisting of pain after joint surgery, arthritis, bursitis, eye infection, eye trauma, burns, cancer, diabetes, and neurological diseases.

10. The method of claim 6, wherein the pain to be treated or prevented is due to a member selected from the group consisting of pain after joint surgery, arthritis, bursitis, eye infection, eye trauma, burns, cancer, diabetes, and neurological diseases.

11. The method of claim 5, wherein said compound is administered orally in an amount of from about 1 to about 250 mg once or up to four times daily.

12. The method of claim 5, wherein said compound is administered parenterally in a solution from about 0.1% to about 5% once or up to four times daily.